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43. (New) A polypeptide according to claim 42 wherein said collagenase is type I collagenase.--

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REMARKS

Applicants canceled claims 5, 8, 28, and 29 without prejudice or disclaimer. Applicants have amended claims 1, 9, 10, 31, 32, and 37. Applicants added new claims 40-43. Support for amended claim 1 and new claims 40-43 can be found in the specification, e.g., at page 44, line 11, to page 45, line 15, and at Figures 2 and 9. The amendments to claims 9, 10, 31, 32, and 37 clarify the claimed subject matter, and do not introduce new matter. Claims 1-4, 6, 7, 9-11, 31, 32, 37, and 40-43 are pending.

Applicants acknowledge the withdrawal of claims 34, 38, and 39 as being drawn to non-elected inventions.

As requested by the Examiner in the May 18, 1998, Office Action, applicants enclose a cleaner copy of pages 100-105. The Examiner had noted that these pages had been canceled in the parent application. Applicants assume that a new copy of those pages is desired since the copy of those pages filed with this Rule 60 application included handwritten notations. The new copy of the claims does not include those notations.

Rejection Under Double-Patenting:

In the May 18, 1998, Office Action, the Examiner rejected claims 1, 2, 4, 6-10, 28, and 29 because allegedly the claims were substantial duplicates. Office Action at page 2, Item No. 2. Specifically, the Examiner alleged that if claim 1 should be found

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allowable, claims 2, 4, 6, 7, 9, and 10 would be found objectionable because the claims were substantial duplicates of claim 1. Id. The Examiner further alleged that if claim 8 should be found allowable, claims 28 and 29 would be found objectionable because they were substantial duplicates of claim 8. Id.

Applicants respectfully traverse the Examiner's objection. The subject matter of claim 1 is not substantially duplicated by dependent claims 2, 4, 6, 7, 9, and 10. Claims 2, 4, 6, 7, 9, and 10 directly or indirectly depend on claim 1, and further restrict the subject matter of claim 1. A dependent claim is a claim that refers "back to and further limit[s] another claim or claims in same application." 37 C.F.R. §1.75(c).

Specifically, Claim 2 restricts the polypeptide of claim 1 to a product of procaryotic or eucaryotic expression of an exogenous DNA sequence. Claim 4 is specifically drawn to a polypeptide expressed from an exogenous DNA sequence which is a cDNA sequence. Claim 6 is directed to a polypeptide expressed from genomic DNA sequences. The polypeptide of claim 7 is expressed using a specific method, i.e., the exogenous DNA sequence is carried on an autonomously replicating DNA plasmid or viral vector. Claims 9 and 10 restrict the claimed polypeptide to one having either the immunological activity or the in vitro biological activity, respectively, of naturally-occurring metalloproteinase inhibitor. Therefore, the invention of claims 2, 4, 6, 7, 9, and 10 have additional limitations not required by claim 1. Accordingly, claims 2, 4, 6, 7, 9, and 10 are not substantial duplicates of claim 1.

Applicants have canceled claims 8, 28, and 29 without prejudice or disclaimer. Accordingly, the objection to these claims is now moot. Applicants respectfully request withdrawal of this objection.

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Rejections Under 35 U.S.C. §112, First Paragraph:

The Examiner rejected claims 1-11, 28, 29, 31, 32, and 37 under §112, first paragraph because allegedly the specification "enabl[ed]...bovine and human TIMP-2 proteins of Figures 1 & 2, respectively [but does] not reasonably...[enable]...biologically functional equivalents, or undescribed allelic variants of these TIMP-2-like proteins." Office Action at page 3, Item No. 3, paragraph 1. The Examiner alleged that "[t]he specification describes a single metalloprotease inhibitor from two distinct species...[but] [n]o written description of what structurally constitutes any other metalloprotease inhibitor, or biologically functional equivalents or allelic variants...is disclosed." Id. at paragraph 2.

Without acquiescing to the Examiner's allegations, applicants have amended claim 1 to recite "a purified and isolated metalloproteinase inhibitor comprising...an amino terminal amino acid sequence comprising at least the amino acid residues 1 to 42 of Figure 2, and...at least one biological activity of naturally-occurring human metalloproteinase inhibitor." The specification would enable one skilled in the art to practice the invention of claim 1.

Further, the Examiner alleged that, though the specification describes pharmaceutical compositions, "it is unknown, and not disclosed, how to determine what constitutes an 'effective amount' of any metalloprotease inhibitor...and when or if 'treatment' would be 'effective'...." Office Action, paragraph bridging pages 3 and 4. "Thus, because the skilled artisan can not successfully determine if any pharmaceutical application of the instant invention works *in vivo* [, and therefore]...claim 32 currently

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merely constitutes an invitation to experiment to discover how to make and use applicants' invention." Id.

Solely to expedite prosecution and not acquiescing to the rejection, applicants have amended claim 32 to recite "[a] composition comprising the polypeptide of claim 1 and a pharmaceutically acceptable diluent, adjuvant, or carrier." The "effective amount" limitation is no longer required in claim 32. Amended claim 32 is not a mere invitation to experiment to discover how to make and use the claimed invention.

The Examiner also alleged that the term "'metalloprotease inhibitor or allelic variants thereof'...does not sufficiently characterize and enable the proteins that are encompassed by the claims...." Office Action at page 4, Item No. 3, paragraph bridging pages 4 and 5. Specifically, the Examiner stated that the "specification does not teach which particular amino acids are critical for any metalloprotease inhibitor protein's function, nor what structural features distinguishes the claimed protein from any other different TIMP-2-like proteins that are 'analogs thereof.'" Id. at page 5. Therefore, the Examiner concluded that the alleged lack of guidance in the specification would prevent one skilled in the art from practicing the claimed invention without undue experimentation.

Without acquiescing to the Examiner's allegations, applicants have canceled claim 8, which was the only previously pending claim that included the term "metalloprotease inhibitor or allelic variants thereof." Accordingly, the basis of this rejection is now moot.

Therefore, in view of the preceding remarks, applicants respectfully request reconsideration and withdrawal of the §112, first paragraph rejection.

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Rejection Under 35 U.S.C. §112, Second Paragraph:

In the Office Action, the Examiner rejected claim 32 because allegedly the claim was indefinite and incomplete. Office Action at page 6, Item No. 4. The Examiner stated that "it is unknown what is envisioned as the intended use of the pharmaceutical compositions, since none is recited." Id.

Solely to expedite prosecution and without acquiescing to this rejection, applicants amended claim 32 so that it no longer specifically recites the term "pharmaceutical composition." Therefore, amended claim 32 definitely and completely describes the claimed invention.

Therefore, applicants respectfully requests the Examiner reconsider and withdraw the pending §112, second paragraph rejection.

Rejections Under 35 U..S.C. §102(b) and (e):

The Examiner rejected claims 1-11, 28, 29, 31, 32, and 37 under 35 U.S.C. §102(b) as allegedly being anticipated by Murray et al. (Murray). Office Action at page 6, Item No. 5. Specifically, the Examiner stated that "Murray et al. [taught] the isolation and partial sequencing of a native bovine metalloprotease inhibitor...that has part of the sequence set forth in Figure 2, and also structurally meets the limitations of a 'naturally occurring allelic variant as set forth in Figure 2'...." Id. Further, the Examiner alleged that at page 4158 and Table III of Murray, a naturally occurring human metalloprotease inhibitor isolated from human skin fibroblasts is described. Id. at page 7.

Applicants have amended claim 1 to recite "[a] purified and isolated metalloproteinase inhibitor comprising a polypeptide...[having] as a mature protein, an

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amino terminal amino acid sequence comprising at least the amino acid residues 1 to 42 of Figure 2, and...at least one biological activity of naturally-occurring human metalloproteinase inhibitor...." By comparing the amino terminal amino acid sequence of Murray with amino acid residues 1 to 42 of Figure 2, one observes that the two sequences differ. Further, Murray neither discusses nor describes a protein having at least one biological activity of naturally-occurring human metalloproteinase inhibitor. Therefore, the protein described in Murray is not the polypeptide described in claim 1. Accordingly, Murray does not anticipate the claimed invention. Applicants request reconsideration and withdrawal of the §102(b) rejection.

The Examiner rejected claims 1-4, 6-11, 28, 29, 31, 32, and 37 under 35 U.S.C. §102(e) as allegedly being anticipated by Stetler-Stevenson et al., U.S. Patent No. 5,595,885 (Stetler-Stevenson). Office Action at pages 7 and 8. The Examiner alleged that Stetler-Stevenson taught "sequencing and cDNA cloning of an immunogenic/HPLC/affinity chromatography-isolated native human metalloprotease inhibitor...that has part or all of the sequence set forth in Figure 2...." Id. at page 8. Further, the Examiner stated that "the courts have held that when a product (i.e., TIMP-2) in a product-by-process claim...is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process." Id.

Stetler-Stevenson claims the benefit of U.S. Serial No. 08/039,525, filed March 29, 1993, which is a continuation application of U.S. Serial No. 07/395,453, filed August 18, 1989, which is a continuation-in-part of U.S. Serial No. 07/380,431, filed July 17,

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1989 (the '431 application), which is a continuation-in-part of U.S. Serial No. 07/326,334, filed March 21, 1989 (the '334 application).

The Examiner apparently accorded Stetler-Stevenson a §102(e) date of March 21, 1989, based on the '334 application's filing date. Although the March 21, 1989, filing date of the '334 application precedes the effective filing date, and the first effective filing date of the present application, May 19, 1989, applicants assert that the Examiner improperly accorded Stetler-Stevenson a §102(e) date of March 21, 1989. The '334 application discusses a metalloprotease inhibitor, but does not disclose the amino terminal amino acid sequence of applicants' claimed polypeptide. Moreover, the '334 application fails to show an amino acid sequence corresponding exactly to Figure 8 of Stetler-Stevenson. In fact, the amino acid sequence shown in Figure 2 of the '334 application (second sequence of the attached Exhibit 1) differs significantly from Figure 8 in Stetler-Stevenson and from amino acids 1-42 in Figure 2 according to the presently claimed invention. After comparing the amino acid sequences of Figure 2 of the '334 application to Figure 2 of the presently claimed invention, one sees that amino acids at positions 34 and 39 of Figure 2 of the presently claimed invention differ from the amino acids at the corresponding positions in Figure 2 of the '334 application. See the attached Exhibit 2: Comparison of the amino acid sequences. Further, the amino acid sequence in Figure 2 of the '334 application does not disclose amino acids 41 and 42 in Figure 2 of the presently claimed invention. Id. Therefore, the '334 application does not disclose amino acids 1-42 of the claimed invention.

In view of the failure to disclose an amino acid sequence according to the present claims, applicants assert that the Examiner may not properly accord Stetler-

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Stevenson a §102(e) date of March 21, 1989, as the basis for maintaining the §102(e) rejection. The next filing date claimed by Stetler-Stevenson is July 17, 1989. Since July 17, 1989, is after May 19, 1989, the first effective filing date of the subject application, the Examiner cannot maintain the §102(e) rejection. Accordingly, applicants respectfully request reconsideration and withdrawal of the Examiner's rejection under §102(e).

If any further extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Amendment, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees and/or petitions required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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By: _____
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Dated: November 17, 1998

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